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FOLEY & LARDNER
WASHINGTON HARBOUR
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER
WALICKA, MALGORZATA A

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1652	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/502,424	KILIAN ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-15,27-40,61,65-93 and 100-107* is/are pending in the application.

4a) Of the above claim(s) *7-10,30,33,35-40,68-70,86-91,100 and 102-107* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6,11-15,27-29,31,32,34,61,65-67,71-85,92,93 and 101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on *25 June 2002* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: copies of the sequence alignements.

The Amendment and Reply under 37 CFR § 1.111 filed on June 25, 2002 as paper No. 17 is acknowledged. The substitute specification is acknowledged. Amendments to the claims have been entered as requested. Claims 3, 16-26, 41-60, 62-64 and 94-99 are cancelled. Claims 1, 4-6, 11, 13, 27, 31, 34, 61, 65, 71, 72, and 101 are amended. Claims 1-2, 4-15, 27-40, 61, 65-93 and 100-107 are pending.

Claims 1-2, 4-6, 11-15, 27-29, 31-32, 34, 61, 65-67, 71-79, 80-85, 92-93 and 101 are readable on the elected species and are the subject of this Office action. Claims 7-10, 30, 33, 35-40, 68-70, 86-91 and 100, 102–107 are withdrawn from consideration as directed to the nonelected invention.

Detailed Office Action

1. Restriction/Election

In their reply, page 5, Applicants disagree that claims 7-10, 30, 33, 35-40, 69-70, 80-90, 91, 93, 102, 104, 105, and 107 are not readable on the elected SEQ ID NO: 45, because the Office did not give any reason for its decision.

Applicants' argument has been fully considered but is found not persuasive as concerns the following claims.

Claims 7-10 are limited to oligonucleotides of the sequence presented in Fig. 1, which is not SEQ ID NO: 45.

Claim 30 is limited to the nucleic acid probe specific for the nucleic acid that has the sequence presented in Fig. 1, which is not SEQ ID NO: 45.

Claim 33 is limited to the primer that specifically amplifies the sequence presented in FIG. 1, which is not SEQ ID NO: 45.

Claims 35-38 are limited to the pair of primers that specifically amplify sequences other that SEQ ID NO: 45.

Claims 39-40 are limited to oligonucleotides that specifically hybridize to sequences other than SEQ ID NO: 45

Claims 69-70 are limited to splice variants that lack or have altered C-terminus of comprising sequence. SEQ ID NO: 45 is lacking region alpha located at nucleotides 2131-2166 of the reference human telomerase, but has normal C-terminus; see description of the sequence in the sequence listing.

Claims 86-91 are limited to the intronic sequences, therefore do not read on SEQ ID NO: 45.

Claims 102-107 are limited to the telomerase variants that have features specifically not found in SEQ ID NO: 45. Said features are: lack a P-loop motif, or C- terminal domain, or an altered C-terminal domain comprising a consensus SH3 binding site.

Applicants' arguments have been found persuasive with regard to the following claims.

Claims 80-85 are directed to many telomerase splicing variants including the variant described by SEQ ID NO: 45. Therefore, the

claims will be, in part concerning SEQ ID NO: 45, the subject of this Office Action.

Claims 92-93 are directed to a pair of oligonucleotide primers that amplify sequence of human telomerase containing specific splice junction. The claims read on SEQ ID NO: 45. The claims will be included in the examination.

Claims 1-2, 4-6, 11-15, 27-29, 31-32, 34, 61, 65-67, 71-79, 80-85, 92-93 and 101 readable on the elected species and are the subject of this Office action. Claims 7-10, 30, 33, 35-40, 68-70, 86-91 and 100, 102–107 are withdrawn from consideration as directed to the nonelected invention.

2. Objections

2.1. Specification

The substitute specification does not comply with sequence rule because Table 1 on page 22 is lacking the sequence identification numbers for described variants. In addition, Table 1 presents the exon/intron content of **ONLY** 16 variants, whereas Applicants claim 35 amino acid sequences of splicing variants; see claims 4, 5, 34, 72. The extension of Table 1 is required so that it presents the intron/exon characteristics of all claimed splice variants together with their sequence identification number.

The specification lacks the list of all the sequences disclosed and respective sequence identification numbers.

The specification lacks the nucleotide sequences of RTase motifs B, C and D.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicants' cooperation is requested in correcting any errors of which applicant may become aware.

2.2. Drawings

The proposed drawing correction and/or the proposed substitute sheets of drawings, filed on June 25, 2002 have been accepted. A proper drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The correction to the drawings will not be held in abeyance.

2.3. Claims

Objections to claims 3-6, 61 and 65 are withdrawn, because the claims have been amended.

Amended claims 13-15 will be examined on merits in this Office Action.

2. Rejections

2.1. 35 USC 101

Rejection of claims 61 and 101 made in the previous Office Action, paper No.13, is withdrawn, because the claims are amended.

2. 2. 35 U.S.C. 112, second paragraph

All rejections made in the previous Office Action, paper No. 13 are withdrawn because the claims have been amended.

New rejection

Claim 4, 5,11-15, 27, 34, 61,65, 71, 72, 80 and 81 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4, 5, 11-15 34, 71 and 72 are rejected because the correct amino acid sequence SEQ ID NO: 46 is unclear. According to the SEQ ID NO: 46 the residue No. 18 is threonine, whereas the 18th codon of the respective encoding DNA sequence, SEQ ID NO: 45, is TAC, which encodes the amino acid tyrosine. As such the correct amino acid present at position 18 of the claimed splice variants is unclear.

Claim 27 recites the phrase "specifically hybridizing to a vertebrate telomerase". The phrase is unclear as there are many vertebrate telomerases. To which must the claimed probe hybridize? If the probe specifically hybridizes to SEQ ID NO:45, hybridization to other human telomerases genes (such as SEQ ID NO:1) or to, for example, to the mouse telomerase gene, is excluded.

Claim 34 is confusing in the recitation of "nucleic acid molecule comprises any of the sequences", as the recited sequences are not nucleotide sequences. A nucleic acid molecule cannot comprise an amino acid sequence.

Claim 61, lines 1-2, "the sequence" lacks antecedent basis. It is suggested that Applicant amend to "a sequence".

Claim 61 recites the phrase "sequence selected from the set consisting of sequences selected from... or region 3 (SEQ ID NO: 30)" is confusing and indefinite. Is the recited set SEQ ID NOs: 23, 25, 27, 29, and 30 or any fragment of SEQ ID NOs:23, 25, 27, 29, and 30? Also, the Markush group should conclude with "and" not "or".

Claims 61, 80 and 81 recite the phrase "or variants thereof" which is indefinite, because the claim does not define the scope of the term "variants".

Claim 65 recites "wherein the reference human telomerase has SEQ ID NO:1". That is confusing as SEQ iD NO:1 is a nucleotide sequence. The phrase should read "wherein reference human telomerse gene has SEQ ID NO:1" or the claim should refer to SEQ ID NO:2 instead of SEQ ID NO:1.

Claim 71, in line 5, recites "to the sequence". It is unclear whether it refers to the splice variant or to the reference telomerase gene.

2.3. 35 U.S.C. 112, first paragraph

2.3.1. Lack of written description

Claims 1, 2, 4, 5-6, 11-15, 61, 65-67, 73-79, 80-85, and 101 remain rejected under 35 USC section 112 first paragraph for failing to provide written description. The rejection is explained in the previous Office Action.

According to Applicants, page 9, line 20, "the genus [genera? MW] in the claims are very well defined in that all of the species encompassed by the claimed genus originate from the disclosed splice variants of human telomerase protein." This

argument is found not persuasive in case of claims 1, 2, 4, 5-6, 11-15, 61, 65-67, 73-79, 80-85, and 101 for the specific reasons mentioned bellow.

As discussed in the written description guidelines (www.uspto.gov), the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between the function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements (i.e. both structural and functional features) possessed by the members of the genus in view of species disclosed. For invention in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one or a few species within the genus.

Claims 1, 2, 4, 65-67 and 73-79 remain rejected because the claims do not disclose the structure of sufficient representative species of any vertebrate or human telomerase toward which the claims are directed. The claims are directed to the genus

of nucleic acid encoding splice variants of the vertebrate/human telomerase. The instant application claims 35 amino acid sequences, SEQ ID NO: 35, 37, 39, 42, 44, 46, 48, 50, 52-54, 56-58, 60-62, 64-66, 68-70, 72-74, 76-78, 80-82 and 84-86 that set forth splice variants of human telomerase gene of SEQ ID NO:1. However, the specification fails to teach splice variants of telomerase genes from other vertebrate than Homo sapiens.

Theoretically, as to the human telomerase as it is disclosed in the specification, i.e., having seven introns, the maximum number of the independently spliced mRNAs is 2^7, i.e.,128 (this number might be higher if all intronic/exonic sequences are not fully characterized). Each of the members of the genus of splice variants has a unique structure. In addition, the members of the genus have diversified functions. They may retain the telomerase function or lose it; and some of the variants may gain a new function. Applicants describe characteristic features of some of the variants on pages 20-21. For example, the splice variant of SEQ ID NO:45 lost the telomerase activity. The protein functions in a dominant negative way causing cellular senescence and telomere shortening. A person skilled in the art recognizes that in the particular case of splice variants, none of the variants, or even tens of them, does not characterize the structure and function of the genus, because one cannot establish only one function/structure relationship for the genus and thus the presence of a large number of species is still deamed to be not representative of the genus. Therefore, any claimed splice variant of the human telomerase is isufficiently described only when its structure is recited by the claim.

Claims 5 and 11-15 are directed to large genus of DNA molecules hybridizing to SEQ ID NO:45. However, no function for the genus is stated and members of the genus would be functionally diverse including species encoding an active telomerase, encoding inhibitors of telomerase activity, species useful in diagnosis of the telomerase related disorders, and species which lack any function. Addition of the functional language would alleviate this rejection.

Claim 6 is directed to a large genus of DNA molecules that hybridize to the complement of one of SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32, 33. The claimed genus lacks sufficient written description, because SEQ ID NOs:18, 23, 25, 27, 29, 30, 32, 33 are not representative species of said genus, as the claimed genus encompasses many members that are highly diverse both in the structure and function. The structure of DNA molecules selected by hybridization to SEQ ID NOs:18, 23, 25, 27, 29, 30, 32, 33 is very diversified. In addition, the claimed genus lacks functional characterization. Intronic sequences such as SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32, 33 do not have a specific biologic activity but may have use as diagnostic probes. However, the sequences selected by hybridization to the complements of intronic sequences may encode the telomerase reverse transcriptiase activity or other specific biologic activities. The telomerase reverse transcriptase activity is not encoded by the intronic sequences or their complements. Thus, the disclosed functions of SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32, 33 are not representative of the function of all members of the claimed genus. Therefore, claim 6 lack both, structural and functional description.

Claim 61 remains rejected because the amended claim does not state the function of the isolated nucleic acid molecule comprising the sequence selected form the group: SEQ ID NO: 23, 25, 27, 29 or 30, or variants thereof, and members of this genus would be functionally diverse including species encoding an active telomerase, encoding inhibitors of telomerase activity, species useful in diagnosis of the telomerase related disorders, and species which lack any function.

Claims 61, 80-85 remain rejected because the claims are lacking written description of function and structure of large genus of the DNA molecules comprising SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32, 33 or variants of such molecules, or a large genus of DNA molecules encoding any of the amino acid sequences of SEQ ID NOs: 24, 26, 28, and 31 or variants thereof.

The claims are directed to the extremely large genus of DNA molecules containing in their sequences those being of SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32, 33. The genus is lacking sufficient functional description. The specification does not contain disclosure of the function of all polynucleotides containing SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32, 33 or encoding SEQ ID NOs:24, 26, 28 and 31. The claimed genus of polynucleotides is highly variable genus encompassing polynucleotides with a wide variety of functions including encoding an active telomerase, encoding inhibitors of telomerase activity, having diagnostic function and species which lack any function. The function of DNA molecules of SEQ ID NO: 18, 23, 25, 27, 29, 30, 32, 33, is to be used as a DNA probe for diagnostic purposes. However, the claims are directed to the genus of which all the species cannot be used as probes for diagnostic purposes.

Other species have a variety of functions, which have not been described. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filled. Amending the claims to recite "an isolated nucleic acid consisting of a nucleotide sequence of SEQ ID NO: 18, 23, 25, 27, 29, 30, 32, 33" or "an isolated nucleotide sequence consisting of that encoding an amino acid sequence selected from the group consisting of SEQ ID NOs: 24, 26, 28, and 31" would overcome the instant rejection.

Claim 101 is rejected because the claim is directed to a genus of DNA molecules lacking the α insert (A motif) for which the structure characteristic is missing in the claim. There are many variants of the telomerase gene of SEQ ID nO:1that are lacking the A motif but retain other introns. The specification teaches several such splice variants in Table 1, page 22, and the data presented indicate that Applicant possess at least 8 variants lacking the A motif, but the total number of such variants is probably greater. Furthermore the instant claim is not limited to splice variants of the gene of SEQ ID NO:1. The structure of one of such variants is given by SEQ ID NO: 45. The specification fails to describe any other representative species by any identifying characteristics or properties other than being a gene encoding human telomerase splice variant lacking a A-motif. Therefore, one skilled in the art is not convinced that Applicants had been in possession of the claimed invention at the time the application was filed.

New rejection

Claim 66 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim is directed to the nucleic acid molecule encoding a splice variant of human telomerase wherein the variant lacks RTase motifs A, B, C, and D. However, the specification is silent about the structure and function of variants lacking motifs A, B, C and D. The claim is directed to the large genus of the variants for which the structure/function is not disclosed. Each of the members of the genus has a unique structure. In addition, the members of the genus may have diversified functions. They may retain the telomerase function or lose it or may gain a new function. Applicants do not describe function and structure of the genus of splice variants lacking motifs A, B, C and D. Even a single representative of the genus is not disclosed.

Because the claimed invention lacks functional and structural characteristics the claimed genus of splice variants, a skilled artisan is not convinced that the inventor(s), at the time the application was filed, had possession of the claimed invention.

2.3.2. Scope of enablement

Rejection of claims 4-6, 11-12, 27-29, 31-32, 66-67 and 72 made in the previous Office Action, paper No. 13, is withdrawn because the claims have been amended.

Applicants, in response to the rejection, paper No. 16 argue, "A large number of nucleic acid molecules with sequence encoding splice variants of telomerase protein

are given in the specification." Also, Applicants' position is "the specification teaches in detail how to obtain the claimed variants." Although the examiner agrees with both statements, the statements are not found persuasive with regards to all of the claims. Claims 1, 2, 61, 65, 73-79, 80-85 and 101 remain rejected under 35 U.S.C. 112, first paragraph for the scope of enablement for the reasons indicated bellow.

Claims 1, 2, and 65, 73-79 remain rejected because the specification, while being enabling for the splice variant of human telomerase gene having SEQ ID NO: 45, as well as other 34 splicing variants of human telomerase, is not enabling for any splice variant of any vertebrate telomerase and any splice variant of human telomerase, or any human telomerase splice variant that lacks RTase motif A.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to the extremely large number of DNA molecules that are encompassed by them.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or

absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompasses any splice variant of telomerase obtained from any vertebrate or respective gene libraries, and any splice variant of human telomerase, or any human telomerase splice variant that lacks RTase motif A.

While methods of gene cloning, sequencing, expressing and testing the function of expressed protein are well known in the relevant art, and skills of the artisans highly developed, identifying all DNA molecules encoding splice variants of all vertabrate telomerases, or encoding all splice variants of human telomerase or all human telomerase splice variant that lack RTase motif A, is outside the realm of routine experimentation. In addition, the probability of success in obtaining the claimed invention is low.

As indicated above in rejection for lack of written description, each of the members of the claimed genus of splice variants genus has a unique structure. In addition, the members of the genus may have diversified functions. They may retain the telomerase function or lose it or may gain a new function. Therefore, in the particular case of splice variants one skill in the art is unable to give a representative description of the genus, even if all members of the genus are identified and characterized. In the instant application Applicants do not describe function and structure of all the members of the genera of splice variants of all vertebrate telomerases, nor all the members of the genus of splice variants of human telomerase

or all splice variants of human telomerase lacking motif A. Because the claimed invention lacks functional and structural characteristics the claimed genera of splice variants, without the further guidance on the part of Applicants as to the source of the telomerase gene, as well as the specific polynucleotide sequence of the splice variant, the experimentation in obtaining the claimed invention left to those in the art is improperly extensive and undue.

Claim 61, 80-85 remain rejected for scope of enablement because the specification, while being enabling for sequences consisting of SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32 and 33, is not enabling for any DNA molecule comprising a sequence from this group of sequences, or a complement or variant thereof; see the above rejection for lack of written description.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to the extremely large number of DNA molecules that are encompassed by them.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the

nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompasses any DNA molecule comprising a sequence from this group of SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32 and 33, or a complement or variant thereof.

While methods of gene cloning, sequencing, as well as synthesizing and modifying are well known in the relevant art, and skills of the artisans highly developed, identifying in biologic or man-made sources, or producing, all DNA molecule comprising a sequence from this group of SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32 and 33, or a complement or any variant thereof, as determined by the language of the claims, is outside the realm of routine experimentation. In addition, the probability of success in obtaining the claimed invention is low.

The examples provided by the disclosure are SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32 and 33 and some splice variant of human telomerase gene containing some of them. The specification fails to disclose any variants of SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32 and 33, neither the specification teach how to modify SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32 and 33 to obtain such variants. Applicants enablement is limited to SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32 and 33, and some splice variants of human telomerase containing these sequences. Thus, Applicants did not provide sufficient guidance how to make the claimed invention. Without the further guidance on the part

of Applicants as to the modification of SEQ ID NO: 18, 23, 25, 27, 29, 30, 32 and 33 the experimentation left to those in the art is improperly extensive and undue.

2.4. 35 USC section 102

In their response to rejection under 35 USC section 102 made in the previous Office Action paper No. 13, Applicants stated, "the '809 patent does not even mention, let alone teach or suggest, splice variant of human telomerase". This argument is not found persuasive in case of claims 1-2,11-15, 65, 73-79, for reasons enumerated below. In addition, intronic sequences as claimed in claims 6, 1-15, 61 and 80-85 are comprised in sequences disclosed by Cech et al, as indicated bellow. Also, Cech et al. in their '809 patent disclose many probes and primers for amplification of the human telomerase DNA. Probes are claimed in claims 27-31 of the instant application, and primers are claimed in claims 34, 92, and 93.

Amended claims 1-2, 4, 6, 11-15, 61, 65, 73-79 and 80-85 are rejected under 35 U.S.C. 102(e) as being anticipated by Cech et al in the US Patent No. 6,166,178, issued December 26, 2000, with priority to Oct. 1996 and US Patent No. 6,093,809 issued on July 25, 2000, with priority to Oct. 1996.

Claim 1-2, 11-15, 65, 73-79, are directed to a DNA molecule encoding a splice variant of vertebrate telomerase, or human telomerase, or a splice variant of reference telomerase wherein the reference telomerase has SEQ ID NO: 1.

Cech et al. disclose a human telomerase splice variant, delta-182 variant (column 13, line 67 and column 20, line 39), having amino acid sequence SEQ ID NO: 5

that is encoded by SEQ ID NO: 4. This splice variant lacks intron β that has in the instant application SEQ ID NO:27, and is located between nucleotides 2286-2469 of the reference telomerase. Although Cech et al do not use the term "splice variant" they contemplate that polypeptides such as delta 182 variant may play a biological role in nature (e.g., in regulation of telomerase expression) and find use as therapeutics (e.g. as dominant-negative products that inhibit function of wild–type proteins). Copies of the relevant pages of the patent and alignement of sequences are attached.

Claim 4 remains rejected as anticipated by Cech et al in the US Patent No. 6,093,809 issued on July 25, 2000, with priority to Oct. 1996. The claim is directed to the DNA molecule encoding a variant of SEQ ID NO: 46 that has at least 75% identity to amino acid sequence of SEQ ID NO: 46.

SEQ ID NO: 224 of the US Patent No. 6,093,809,encodes a variant of SEQ ID NO: 46 that has SEQ ID NO: 225 in the patent and has more than 75% amino acid identity to SEQ ID NO: 46; see the enclosed alignment.

Claim 6, 11-15, 61 are rejected as being anticipated by Cech et al in the US Patent No. 6,166,178, issued December 26, 2000, with priority to Oct. 1996 and the US Patent No. 6,093,809 ('809) issued on July 25, 2000, with priority to Oct. 1996.

The claims are directed to an isolated nucleic acid which will hybridize to a nucleic acid molecule comprising SEQ ID NO: 18, 25 and 27 or encoding amino acid sequence of SEQ ID NOs: 26 and 27and/or to fragments of these sequences.

SEQ ID NO: 599 of the US Patent No. 6,166,178 contains in position 31-134 nucleotides identical to nucleotides 1-104 of SEQ ID NO: 18 of the instant application.

SEQ ID NO: 224 of US Patent No. 6,093,809 contains in positions 2136-2221 the sequence identical to the whole sequence of SEQ ID NO: 25 of the instant application. SEQ ID NO: 25 encodes the amino acid sequence of SEQ ID NO: 26.

SEQ ID NO: 224 of US Patent No. 6,093,809 contains in positions 2342-2523 the sequence identical to the whole sequence of SEQ ID NO: 27 of the instant application. SEQ ID NO:27 encodes the amino acid sequence of SEQ ID NO: 28.

New rejection

Claims 27-29, 31-32, 34, 80-85 and 92 are rejected as being anticipated by Cech et al in the US Patent No. 6,166,178, issued December 26, 2000, with priority to Oct. 1996 and the US Patent No. 6,093,809 ('809) issued on July 25, 2000, with priority to Oct. 1996.

Claims 27-29 and 31 are directed to a nucleic acid probe that is specifically hybridizing to a nucleic acid molecule encoding a vertebrate telomerase.

Cech et al. provide extensive disclosure regarding expression of telomerase, primers, hybridization, preparing oligonucleotide fragments of telomerase encoding DNA for the purposes of detecting the human telomerase gene product such as those detected by amplifying the gene and detecting amplification products (see US Patents No. 6,166,178; column 4 line 28, column 5 line 65, column 6 line 1, section *Illustrative Oligonucleotides*, column 26, Table 2, columns 27-35 presenting tens of primers, Table 10 oligonucleotides used in the sequence of human telomerase DNA, columns 61 and 62; see also US Patent No. 6,093,809, section *Uses of the Polynucleotides Encoding*

Telomerase Subunit Proteins, column 32 line 30, list of primers in Table 3 in Example 18, column 58-59 of the US Patent No. 6,093,809). Cech et al. clearly suggests making such probes and primers from all regions of telomerase encoding nucleic acids, including exons and introns.

Claims 32 and 34 are directed to a pair of primers capable of specifically amplifying all or a portion of a nucleic acid molecule encoding human telomerase, or its splice variants. Cech et al list in Table 3, column 58, of the US Patent No. 6,093,809, thirteen primers that were used to identify the human telomerase sequence. The primers having sequence identification numbers 87-99 in the patent and cover the following nucleotides of SEQ ID NO: 1 of the instant application: 1972-1990, 2599-2617, 2586-2682, 3597-3615, 3607-3625, 2184-2202, none, 3003-3021, 3267-3285, 3239-3257, 3438-3454, 3554-3571, 1895-1913, respectively. In addition, Cech et al. in the US Patent 6,166,178 teach in example 3 entitled *Characterization of an hTRT Intronic Sequence,* in column 162 and 163, primers that may be used in amplification of intron Y (see Table 10, column 27-29), localized between nucleotides 222-223 of the reference SEQ ID NO: 1 of the instant application. Also, Cech et al teach in the US Patent 6,166,178, column 112, Table 4 giving the primers sequences, how to amplify the delta 182 variant of human telomerase that is a variant lacking intron β.

Claims 80-85 are directed to an isolated nucleic acid molecule comprising SEQ ID NO: 18, 25 and 27 or encoding amino acid sequence of SEQ ID NOs: 26 and 27.

SEQ ID NO: 599 of the US Patent No. 6,166,178 contains in position 31-134 nucleotides identical to nucleotides 1-104 of SEQ ID NO: 18 of the instant application.

SEQ ID NO: 224 of US Patent No. 6,093,809 contains in positions 2136-2221 the sequence identical to the whole sequence of SEQ ID NO: 25 of the instant application. SEQ ID NO: 25 encodes the amino acid sequence of SEQ ID NO: 26.

SEQ ID NO: 224 of US Patent No. 6,093,809 contains in positions 2342-2523 the sequence identical to the whole sequence of SEQ ID NO: 27 of the instant application. SEQ ID NO: 27 encodes the amino acid sequence of SEQ ID NO: 28.

Claim 92 is directed to a pair of oligonucleotide primers that amplify sequence of human telomerase containing a splice junction, wherein the primer pair flanks nucleotide 222. Cech et al. in the US Patent 6,166,178 teach in example 3 entitled *Characterization of an hTRT Intronic Sequence,* in column 162 and 163, how to amplify the splice junction for the intron having the sequence of nucleotides 31-134 of SEQ ID NO: 599 which is SEQ ID NO: 18 of the instant application. The intron is localized at position 222 of the reference SEQ ID NO: 1 of the instant application. The primers used by Cech et al. are limited to those located from nucleotide 111 to nucleotide 3772 of the reference telomerase sequence.

2.4. 35 USC section 103 - new rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 93 is rejected under 35 U.S.C. 103(a) as being unpatentable US Patent No. 6,166,178 issued to Cech et al and further in the view of the common knowledge in the molecular biology.

The claim is directed to a pair of oligonucleotides primers that amplify sequence of human telomerase containing a splice junction wherein only one primer of each primer pair flanks nucleotides 222, and the other primer of the pair has the sequence corresponding to all or a portion of one of the SEQ ID NOs: 18, 23, 25, 27, 29, 30, 32 or 33.

Nucleotides 1-104 of SEQ ID NO: 18 encoding intron Y of the instant application are nucleotides 31-134 of SEQ ID NO: 599 of the US Patent No. 6,166,178. Cech et al. in the US Patent 6,166,178 teach in Example 3 entitled *Characterization of an hTRT Intronic Sequence*, in column 162 and 163, how to amplify the splice junction for the intron having the sequence of nucleotides 31-134 of SEQ ID NO: 599 which is SEQ ID NO: 18 of the instant application. The intron is localized at position 222 of the reference SEQ ID NO: 1 of the instant application. The primers used by Cech et al. are limited to those located from nucleotide 111 to nucleotide 3772 of the reference telomerase sequence. Cech et al. do not specifically teach the use of a fragment, or the whole intron Y as a second primer in the pair to amplify the splice junction at the borders of intron Y.

However, it would have been obvious to one of ordinary skill in the art, having the identified sequence of intron Y and its location in the telomerase gene, as taught by

Cech et al., to use a primer flanking the 5' border of intron Y, as taught by Cech in Example 3, and replace other primers of the pairs used by Cech in this example by the whole intron Y sequence or its fragment. The motivation would be to use these pair pf primers in determining the pattern of expression of human telomerase in human cancers or aging related diseases, for diagnostic purposes (see US Patents No. 6,166,178; column 4 line 28, column 5 line 65, column 6 line 1, section *Illustrative Oligonucleotides*.

The expectation of success in selection of primers would be 100%, and the expectation of success in amplification very high, because amplification of desired DNA sequences is a routine in the art.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

In addition, claims 93 is rejected under 35 U.S.C. 103(a) as being unpatentable over combination of:

(1) US Patents No. 6,166,178, fragments of SEQ ID NO: 599;

(2) SEQ ID NO: 224 of the US Patent No. 6,093,809, fragments of SEQ ID NO: 224 which, starting from its position No. 36, is identical to SEQ ID NO: 1 in the instant application;

(3) primers identified by SEQ ID NOs: 87-99 disclosed in the US Patent No. 6,093,809, Table 3 in Example 18, column 58-59; and

(3) Adams et al. supra, fragments of AA311750 locus.

The US Patents No. 6,166,178 teaches (column 162, example 3 entitled Characterization of an hTRT Intronic Sequence) how to amplify, using appropriate fragment of SEQ ID NO: 224, the two splice junctions surrounding the intron identified in the instant application by SEQ ID NO: 18.

Cech clearly suggest making probes and primers from all regions of telomerase encoding nucleic acids, including exons and introns; see supra .

The patents, or Adams et al, do not teach:

(a) how to combine two fragments of SEQ ID NO: 224, or primers from the group of SEQ ID NOs: 87-99, so that the said two fragments or primers formed a pair useful in amplifying the sequences of human telomerase containing splice junction limiting introns identified by SEQ ID NO: 23, 25, 27, 29, 30, 32, and 33 of the instant application.

(b) how to select fragments of SEQ ID NO: 224, or primers from the group of SEQ ID NO: 87-99, so that the first primer of each pair comprised sequence 5' or 3' to nucleotide 222, 1950, 2131-2166, 2287-2468, 2843 or 3157 of SEQ ID NO: 1 of the instant application, and the second primer of the pair comprised sequence corresponding to all of SEQ ID NO: 18, or all or a portion of SEQ: 23, 25, 27, 29, 30, 32, 33.

However, in the light of extensive teaching of Cech et al., it would have been obvious to one having ordinary skill in the art, having the sequences of SEQ ID NO: 224 or of Adams to make fragments from SEQ ID NO: 224 or from AAA311750 locus so that they consisted of contiguous nucleotides of SEQ ID NO: 25, 27 and 29 that may be

used as primers. It would also be obvious to combine two fragments in a pair of primers or two select two primers from the group of primers having SEQ ID NO: 87-99 or two combine a fragment of SEQ ID NO: 224 with one of the primers from those having SEQ ID NOs: 87-99, so that they comprised sequence 5' or 3' to nucleotides, 1950, 2131-2166, 2287-2468, 2843 or 3157 of SEQ ID NO: 1 of the instant application. For example, primers SEQ ID NO: 87 (nucleotides 1972-1990 of SEQ ID NO: 1 of the instant application) and SEQ ID NO: 92 (nucleotides 2184-2202) flank oligonucleotides 2131-2166 as recited by the clam.

The expectation of success in selection and combination of selected primers into a pair would be 100%.

The motivation, also suggested by Cech et al, supra, would be to determine the pattern of expression of human telomerase in human cancers or aging related diseases, for diagnostic purposes. The expectation of success in the performance the required amplification is very high.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

2. 5. Double patenting

2. 5. 1. Obviousness type provisional double patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. See In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1,2,4-6, 11-15, 27-29, 31, 32, 34, 61, 65-67, 71-79, 80-85, 92-93 and 101 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 65-87 of copending Application No. 09/108,401 ('401). Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the respective sets of claims is the same, but scopes are different. Each of the applications is claiming overlapping subject matter including nucleic acids of SEQ ID NO:45, fragments thereof, vectors, and host cells comprising these nucleic acids.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

3. Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.
Art Unit 1652
Assistant Patent Examiner

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600